08/872,527

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     for archive news)
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      Set  Items  Description
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? b 410

>>>'IALOG' not recognized as set or accession number
? set hi ;set hi

       12jul99 08:06:40 User208709 Session D445.1
            $0.27    0.084 DialUnits File1
     $0.27  Estimated cost File1
            FTSNET   0.016 Hrs.
     $0.27  Estimated cost this search
     $0.27  Estimated total session cost   0.084 DialUnits

File 410:Chronolog(R)  1981-1999 May/Jun
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       12jul99 08:06:51 User208709 Session D445.2
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     $0.00  Estimated cost File410
            FTSNET   0.003 Hrs.
     $0.00  Estimated cost this search
     $0.27  Estimated total session cost   0.125 DialUnits

File 155:MEDLINE(R)  1966-1999/Aug W4
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*File 155: reloaded, note accession numbers changed.

      Set  Items  Description
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? s bispecific(w)antibod? and arm?

            798  BISPECIFIC
         516748  ANTIBOD?
            507  BISPECIFIC(W)ANTIBOD?
          60050  ARM?
      S1     22  BISPECIFIC(W)ANTIBOD? AND ARM?
? t s1/7/1-22


 1/7/1
DIALOG(R)File 155:MEDLINE(R)
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09988111   99277553
  Dual specificity antibodies using a double-stranded oligonucleotide
bridge.
  Chaudri ZN; Bartlet-Jones M; Panayotou G; Klonisch T; Roitt IM; Lund T;
Delves PJ
  Department of Immunology, University College London, The Windeyer
Institute for Medical Sciences, UK.
  FEBS Lett (NETHERLANDS)  Apr 30 1999,  450 (1-2) p23-6,  ISSN 0014-5793
Journal Code: EUH
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Languages: ENGLISH
Document type: JOURNAL ARTICLE
The covalent conjugation of oligonucleotides to antibody Fab' fragments was optimized by using oligonucleotides modified with a hexaethylene linker **arm** bearing three amino groups. One oligonucleotide was coupled to antibody of one specificity and a complementary oligonucleotide to antibody of a second specificity. The antibodies were then allowed to hybridize by base pairing of the complementary nucleotide sequences and the generation of **bispecific antibody** was analyzed on SDS-PAGE and confirmed using BIAcore analysis. The strategy of complementary oligonucleotide-linked bispecific molecules is not limited to antibodies but is applicable to linking any two molecules of different characteristics.

1/7/2
DIALOG(R)File 155:MEDLINE(R)

09566731 98312581
Anti-CD3-based **bispecific antibody** designed for therapy of human B-cell malignancy can induce T-cell activation by antigen-dependent and antigen-independent mechanisms.
Link BK; Kostelny SA; Cole MS; Fusselman WP; Tso JY; Weiner GJ
Department of Internal Medicine, University of Iowa Cancer Center, University of Iowa College of Medicine, Iowa City, USA. brian-link@uiowa.edu
Int J Cancer (UNITED STATES) Jul 17 1998, 77 (2) p251-6, ISSN 0020-7136 Journal Code: GQU
Contract/Grant No.: R01 CA67368, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Anti-CD3 x anti-B-cell antigen bispecific monoclonal antibodies (bsAbs) can redirect T-cell-mediated lysis toward malignant B cells. Clinical trials with CD3-based bsAbs have shown toxicity in patients which is likely related to nonspecific T-cell activation and targeting. Our current studies were designed to explore the mechanisms responsible for the observed in vivo toxicity by evaluating the immunologic effects of 2 different bsAb preparations in vitro. 1D10 was used as the tumor specific **arm** of the bsAbs. This antibody reacts with a variant of HLA-DR found on a majority of pre-B- and B-cell malignancies, and normal B cells in some individuals. Anti-CD3 served as the T-cell specific **arm** . A 1D10 x anti-CD3 bispecific IgG (bsIgG) produced using the hybrid-hybridoma method was compared to a 1D10 x anti-CD3 bispecific F(ab')2 [bsF(ab')2] produced using the leucine zipper technique. In cytotoxicity assays, both bsIgG and bsF(ab')2 induced lysis by pre-activated T cells of 1D10 (+) malignant B cells. bsIgG at high concentrations also induced lysis of 1D10 (-) tumor cells, while bsF(ab')2 did not. Proliferation of T cells induced by bsIgG and bsF(ab')2 was also evaluated. Both forms of bsAbs induced T-cell proliferation in the presence of antigen (+) Raji cells, while only bsIgG did so in the presence of antigen (-) malignant B cells. bsF(ab')2 induced T-cell activation in the absence of any tumor cells when testing was performed on samples where the 1D10 target antigen was present on normal peripheral blood B cells. We conclude that non-specific T-cell activation from bsAbs can occur in an antigen-independent manner due to the Fc/Fc receptor (FcR) interaction, or in an antigen-dependent manner when antigen is expressed on normal or tumor cells. Both mechanisms may have been responsible for the toxicity observed in prior clinical studies.

1/7/3

DIALOG(R)File 155:MEDLINE(R)

09466609 98208286

Generation of HER-2/neu-specific cytotoxic neutrophils in vivo: efficient **arming** of neutrophils by combined administration of granulocyte colony-stimulating factor and Fcgamma receptor I **bispecific antibodies**.

Heijnen IA; Rijks LJ; Schiel A; Stockmeyer B; van Ojik HH; Dechant M; Valerius T; Keler T; Tutt AL; Glennie MJ; van Royen EA; Capel PJ; van de Winkel JG

Department of Immunology, University Hospital Utrecht, The Netherlands.

J Immunol (UNITED STATES) Dec 1 1997, 159 (11) p5629-39, ISSN 0022-1767 Journal Code: IFB

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Abs are able to induce inflammatory antitumor responses by recruiting IgG Fc receptor (FcgammaR)-bearing cytotoxic effector cells. We recently described the capacity of the high affinity FcgammaRI (CD64) to trigger cytotoxic activity of neutrophils (PMN) during granulocyte CSF (G-CSF) treatment. To take advantage of FcgammaRI as a cytotoxic trigger molecule on PMN, two Ab constructs were prepared. We show that a chimeric human IgG1 Ab (Ch520C9) and an anti-FcgammaRI bispecific Ab (BsAb; 22x520C9), both directed to the proto-oncogene product HER-2/neu, interact with FcgammaRI. In addition, both Ab constructs mediate enhanced lysis of HER-2/neu-expressing tumor cells by G-CSF-primed PMN. However, engagement of FcgammaRI by Ch520C9 was inhibited by human serum IgG, thereby abrogating the enhanced Ch520C9-mediated cytotoxicity. BsAb 22x520C9, which binds FcgammaRI outside the ligand binding domain, effectively recruits the cytotoxic potential of FcgammaRI on G-CSF-primed PMN regardless of the presence of human serum. These results indicate that under physiologic conditions, serum IgG impairs activation of FcgammaRI-mediated cytotoxicity by conventional antitumor Abs. The IgG blockade can be circumvented with anti-FcgammaRI BsAbs. Using human FcgammaRI transgenic mice we demonstrate that BsAb 22x520C9 is able to engage FcgammaRI in vivo. BsAb 22x520C9 injected i.v. was readily detected on circulating PMN of G-CSF-treated transgenic animals. In addition, we showed that PMN remain **"armed"** with BsAb 22x520C9 during migration to inflammatory sites, and that after isolation such PMN specifically lyse HER-2/neu-expressing tumor cells. These results point to the possibility of targeting anti-FcgammaRI BsAbs to G-CSF-primed PMN in vivo, endowing them with specific anti-tumor activity.

1/7/4

DIALOG(R)File 155:MEDLINE(R)

09284013 97462661

HLA class II antibodies recruit G-CSF activated neutrophils for treatment of B cell malignancies.

Valerius T; Elsasser D; Repp R; Van de Winkel JG; Gramatzki M; Glennie M

Department of Medicine III, University Erlangen, Nurnberg, Germany. Thomas.Valerius@med3.med.uni-erlangen.de

Leuk Lymphoma (SWITZERLAND) Jul 1997, 26 (3-4) p261-9, ISSN 1042-8194 Journal Code: BNQ

Languages: ENGLISH

Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

Monoclonal antibodies offer the potential to improve specificity of oncological therapy. However, future success in the clinic depends on enhancing antibody effector functions. Here, we suggest that target antigen selection may influence recruitment of effector cells for antibody therapy,

and may improve the outcome of antibody treatment in patients. Comparing a wide range of antibodies to different B cell antigens, we found most were able to mediate antibody dependent cellular cytotoxicity (ADCC) with blood mononuclear cells (MNC). In direct contrast, however, polymorphonuclear granulocytes (PMN) from the same donors showed ADCC only with HLA class II antibodies. Based on this observation, we propose a therapeutic strategy with a combination of HLA class antibodies and G-CSF, the latter being required to increase number and activational state of neutrophils. In particular, we suggest using **bispecific antibodies** (BsAb) in which one **arm** binds to HLA class II on tumor cells, and the second to FcgammaRI on activated effector cells. The clinical potential of this approach for the treatment of B cell malignancies looks most attractive. (59 Refs.)

1/7/5
DIALOG(R)File 155:MEDLINE(R)

09227890 96199419
Bispecific-**armed** , interferon gamma-primed macrophage-mediated phagocytosis of malignant non-Hodgkin's lymphoma.
Ely P; Wallace PK; Givan AL; Graziano RF; Guyre PM; Fanger MW
Department of Medicine, Dartmouth Medical School, Lebanon, NH 03756, USA.
Blood (UNITED STATES) May 1 1996, 87 (9) p3813-21, ISSN 0006-4971 Journal Code: A8G
Contract/Grant No.: AI-19053, AI, NIAID; CA-09658, CA, NCI; CA-23108, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
To show that macrophages can be effectively targeted against malignant B cells, **bispecific antibodies** (BsAb) were constructed from two antibodies having specificity for the high-affinity Fc receptor for IgG (Fc gamma RI/CD64) and the B-cell differentiation antigens CD19 and CD37. Using a flow cytometry-based assay and confocal imaging, we show that these constructs mediated significant phagocytosis of B lymphocytes by macrophages that could be enhanced with interferon gamma (IFN gamma) and IFN gamma in combination with macrophage colony-stimulating factor. BsAb-dependent phagocytosis was triggered through Fc gamma RI and could be blocked only by using F(ab')2 fragments from the parent molecule or by cross-linking Fc gamma RI. BsAb-dependent phagocytosis was not blocked by antibodies to the other Fc receptors, Fc gamma RII and Fc gamma RIII. Because these antibody constructs bind to an epitope outside the Fc gamma RI ligand binding site, we show that autologous serum, polyclonal IgG, and monomeric IgG1 did not block BsAb-dependent phagocytosis, whereas autologous serum and the IgG fractions blocked parent molecule monoclonal antibody-dependent phagocytosis due to the avid binding of monomeric IgG to Fc gamma RI. Finally, BsAb-mediated phagocytosis was effective against the malignant B cells of patients with mantle cell lymphoma, prolymphocytic leukemia, and chronic lymphocytic leukemia. Based on these studies, we propose that BsAbs may provide an effective means of immunomodulation for patients with B-cell malignancies.

1/7/6
DIALOG(R)File 155:MEDLINE(R)

09171022 97362800
Retargeting serum immunoglobulin with bispecific diabodies.
Holliger P; Wing M; Pound JD; Bohlen H; Winter G

MRC Centre for Protein Engineering, Cambridge, UK. ph1@mrc-lmb.cam.ac.uk
Nat Biotechnol (UNITED STATES) Jul 1997, 15 (7) p632-6, ISSN 1087-0156 Journal Code: CQ3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Monospecific antibody fragments produced in bacteria lack the Fc portion of antibodies, and are therefore unable to recruit natural effector functions. We describe the use of a **bispecific antibody** fragment (diabody) to recruit the whole spectrum of antibody effector functions by retargeting serum immunoglobulin (Ig). One **arm** of the diabody was directed against the target antigen, and the other against the serum Ig. The bispecific diabodies were able to recruit complement, induce mononuclear phagocyte respiratory burst and phagocytosis, and promote synergistic cytotoxicity towards colon carcinoma cells in conjunction with CD8+ T-cells. Further, by virtue of binding to serum Ig their half-life (beta-phase) was increased fivefold compared to a control diabody of the same molecular weight. Such bispecific diabodies may provide an attractive alternative to monoclonal antibodies for serotherapy.

1/7/7
DIALOG(R)File 155:MEDLINE(R)

09110194 97336010
Trioma-based vaccination against B-cell lymphoma confers long-lasting tumor immunity.
Mocikat R; Selmayr M; Thierfelder S; Lindhofer H
GSF-Institut fur Immunologie, Munchen, Germany. mocikat@gsf.de
Cancer Res (UNITED STATES) Jun 15 1997, 57 (12) p2346-9, ISSN 0008-5472 Journal Code: CNF
Languages: ENGLISH
Document type: JOURNAL ARTICLE
A major goal of tumor immunotherapy is the induction of a systemic immune response against tumor antigens such as the tumor-specific immunoglobulin idiotype (Id) expressed by lymphomas of the B-cell lineage. We describe an approach based on specific redirection of the tumor Id toward professional antigen-presenting cells (APCs), thereby overcoming the inefficient presentation on the parental transformed B cell. Lymphoma cells are fused to a xenogeneic hybridoma cell line that secretes an antibody against a surface molecule on APCs. Due to preferential assembly between heavy and light chains of antibodies of different species-origin, the resulting "trioma" cells produce at high yield a **bispecific antibody** containing the lymphoma Id and the APC-binding **arm**, which redirects the Id to APCs. Processing and presentation of the Id will lead to T-cell activation. An absolute requirement for inducing a complete tumor protection was the immunization with antibody-secreting trioma cells as a cell-based vaccine instead of the soluble **bispecific antibody**. Tumor immunity was specific and long-lasting. Both CD4+ and CD8+ T cells were necessary for inducing tumor immunity.

1/7/8
DIALOG(R)File 155:MEDLINE(R)

08916485 97131784
Bispecific antibodies target operationally tumor-specific antigens in two leukemia relapse models.
Lindhofer H; Menzel H; Gunther W; Hultner L; Thierfelder S
Forschungszentrum fur Umwelt und Gesundheit (GSF)-Institut fur

Immunologie, Munich, Germany.
Blood (UNITED STATES) Dec 15 1996, 88 (12) p4651-8, ISSN 0006-4971
Journal Code: A8G
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Despite improved procedures in chemotherapy and bone marrow transplantation (BMT), post-BMT leukemia relapse rates have remained rather constant in the last decade. Immunotherapy with monoclonal or **bispecific antibodies** (bsAb) is a promising approach to improve this situation, but is hampered by the absence of tumor-specific antigens on the majority of tumors. To evade this problem, we developed a new tumor-specific approach in which **bispecific antibodies** exploit chimerism after allogeneic BMT by redirecting donor T cells against recipient-specific antigens on tumor cells. Two different leukemia relapse models were established using a T-cell lymphoma (ST-1) and a B-cell lymphoma (BCL1) to evaluate the efficiency of such a therapy. In these experiments, irradiated BALB/c (Thy-1.2+, I-Ad) mice were transplanted with C57BL/6 Thy-1.1 (I-Ab) BM cells under the protection of graft-versus-host disease-preventing monoclonal antibodies. Forty-five days after BMT, the chimeric mice were injected with either 2 x 10(4) recipient-type, Thy-1.2+, CD3- ST-1 cells or major histocompatability complex (MHC) class II+ (I-Ad)-BCL1 cells. Four days later, the mice were treated with 8 microg bsAb G2 (anti-CD3 x anti-Thy-1.2) or 10 microg (+10 microg, day 6) bsAb BiC (anti-CD3 x anti-I-Ad), respectively. These combinations guaranteed exclusive binding of the bsAbs target **arms** to tumor cells, leaving the surrounding, donor-type hematopoietic cells unbound. Compared with the parental antibodies, the bsAbs markedly reduced tumor mortality. Between 34% and 83% of mice survived in the bsAb groups compared with 0% of the control groups treated with parental antibodies, clearly documenting the benefit of the redirection principle. Furthermore, cytokine release (interleukin-6) after anti-CD3 antibody or bsAb treatment was decreased by administering a low-dose antibody preinjection. We have shown (1) that 6 weeks after BMT, when donor T-cell reconstitution is still in progress, T-cell-redirecting bsAb are clearly superior to parental antibodies in terms of tumor cell elimination; and (2) that the polymorphism of a common antigen such as Thy-1 or a clinically more relevant target antigen such as MHC class II can be used as an operational tumor-specific antigen after allogeneic BMT.

1/7/9
DIALOG(R)File 155:MEDLINE(R)

08872331 96365778
Cytotoxicity of B72.3XOKT3 **bispecific antibody** recognizing human colon cancer.
Shpitz B; Stern H; Sandhu JS; Reilley RM; Tropak MB; Jansz G; Xu J; Gallinger S
Department of Surgery, Mount Sinai Hospital, Toronto, Ontario, Canada.
J Surg Res (UNITED STATES) Feb 15 1996, 61 (1) p134-8, ISSN 0022-4804
Journal Code: K7B
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Bispecific monoclonal antibodies can be used to redirect peripheral blood lymphocytes against tumor cells. In the present study, a murine bispecific monoclonal antibody was developed using somatic hybrydization. The antibody has two different binding **arms**: one **arm** directed against human CD3 receptor expressed on T-lymphocytes and the other against tumor associated glycoprotein TAG-72, expressed on human carcinomas, such as colon, breast, and pancreas. Partially purified antibody was capable of

inducing human T-cell proliferation and preventing growth of colon cancer cell line in nu/nu mice in a tumor neutralization assay.

1/7/10
DIALOG(R)File 155:MEDLINE(R)

08864563 97074939
A mouse/human-chimeric **bispecific antibody** reactive with human carcinoembryonic antigen-expressing cells and human T-lymphocytes.
Kuwahara M; Kuroki M; Arakawa F; Senba T; Matsuoka Y; Hideshima T; Yamashita Y; Kanda H
First Department of Biochemistry, School of Medicine, Fukuoka University, Japan.
Anticancer Res (GREECE) Sep-Oct 1996, 16 (5A) p2661-7, ISSN 0250-7005
Journal Code: 59L
Languages: ENGLISH
Document type: JOURNAL ARTICLE
A mouse/human-chimeric **bispecific antibody**, designated CBA-CEACD3, with dual specificities for carcinoembryonic antigen (CEA) and CD3, was generated by chemical cross-linking of a chimeric antibody specific for CEA to another chimeric antibody against CD3. Flow cytometric analysis showed that CBA-CEACD3 can bind specifically to cells expressing CEA and to normal human peripheral blood mononuclear cells (HPBMCs) bearing CD3, respectively. Furthermore, a cell to cell adhesion analysis by a colorimetric assay using the dye 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) demonstrated that CBA-CEACD3 is able to bind CEA-producing cells to CD3-expressing cells, suggesting that both **arms** of CBA-CEACD3 are simultaneously working and can retarget T-cells to the tumor. In an additional colorimetric assay using MTT, this antibody was shown to effectively mediate CEA-expressing tumor cell killing by freshly isolated HPBMCs. Together these results demonstrate that this chimeric **bispecific antibody** may serve as a potentially useful immunotherapeutic reagent for human CEA-producing cancers.

1/7/11
DIALOG(R)File 155:MEDLINE(R)

08782381 96288887
A new in vitro model of specific targeting therapy of cancer: retargeting of PWM-LAK cells with **bispecific antibodies** greatly enhances cytotoxicity to hepatocellular carcinoma.
Saijyo S; Kudo T; Katayose Y; Saeki H; Chiba N; Suzuki M; Tominaga T; Matsuno S
First Department of Surgery, Tohoku University School of Medicine, Sendai, Japan.
Tohoku J Exp Med (JAPAN) Feb 1996, 178 (2) p113-27, ISSN 0040-8727
Journal Code: VTF
Languages: ENGLISH
Document type: JOURNAL ARTICLE
For the purpose of establishing a new in vitro model of adoptive immunotherapy, we synthesized two kinds of **bispecific antibodies** (BsAbs), i.e., (OK x L) BsAbs constructed with both OKT-3 (anti-CD3) and L-7-6 (anti-HCC), and (3G x L) BsAbs constructed with 3-G-8 (anti-CD16) and L-7-6 antibodies. These two BsAbs, having pairs of binding **arms** on their single molecule, showed similar binding to target cells as the parental monoclonal antibodies (OKT-3, 3-G-8 and L-7-6), when examined with FACS. Newly devised in vitro cytotoxicity tests revealed that

LAK or PWM-stimulated LAK (PWM-LAK) cells did not show any significant cytotoxic activity to HCC cells, while both effector cells equally showed greatly enhanced cytotoxicity to HCC even at a low effector/target (0.3) in the presence of BsAbs (OK x L) for the efficient retargeting of the effector cells. Inasmuch as PWM-LAK cells proliferate in vitro 3-5 times faster than LAK cells, adoptive immunotherapy using PWM-LAK cells in combination with (OK x L) BsAbs should be very promising.

1/7/12
DIALOG(R)File 155:MEDLINE(R)

08780184 96388294
Response of B-cell lymphoma to a combination of **bispecific antibodies** and saporin.
French RR; Bell AJ; Hamblin TJ; Tutt AL; Glennie MJ
Lymphoma Research Unit, Tenovus Research Laboratory, Southampton General Hospital, U.K.
Leuk Res (ENGLAND) Jul 1996, 20 (7) p607-17, ISSN 0145-2126
Journal Code: K9M
Languages: ENGLISH
Document type: CLINICAL TRIAL; JOURNAL ARTICLE
Observations are described using a combination of two bispecific F(ab')2 antibodies (BsAb) to deliver the ribosome-inactivating protein, saporin, in the treatment of low-grade, end-stage, B-cell lymphoma. Two BsAb were used, each having one **arm** directed at saporin and one at the CD22 on target B cells. The BsAb, however, recognized different, non-overlapping epitopes on each molecule, a strategy which permits high-avidity double attachment of saporin to the target. The BsAb and saporin were pre-mixed at a molar ratio of 3:1 24 h before treatment and infused intravenously over a period of 1 h. Five patients have been treated, mostly with weekly doses of between 2 and 4 mg of saporin for a period of up to 6 weeks. Toxicity was minimal. Three complained of weakness and myalgia for 1 to 2 days after treatment, without objective neurological deficit or rise in serum creatine kinase. One patient produced an anti-mouse Fab' and an anti-saporin response. All patients showed a rapid and beneficial response to treatment. When present, circulating tumor cells were cleared (4/4 patients), ascitic and pleural effusions were eliminated (2/2 patients) and one patient with splenomegaly showed a marked reduction in tumor bulk. Malignant lymph nodes showed significant, but partial, shrinkage in all patients and finally marrow responded well with tumor clearance in biopsy material and impressive resolution of pancytopenia in some patients. While these responses were mainly short-lived, with tumor progression once the treatment was stopped, their speed and magnitude, and the relative lack of associated toxicity warrants further study of this treatment to determine maximum tolerated doses and therapeutic utility.

1/7/13
DIALOG(R)File 155:MEDLINE(R)

08434716 96041250
Comparison of the performance of anti-CD7 and anti-CD38 **bispecific antibodies** and immunotoxins for the delivery of saporin to a human T-cell acute lymphoblastic leukemia cell line.
Flavell DJ; Cooper S; Okayama K; Emery L; Flavell SU
Simon Flavell Leukaemia Research Laboratory, University Department of Pathology, Southampton General Hospital, U.K.
Hematol Oncol (ENGLAND) Jul-Aug 1995, 13 (4) p185-200, ISSN 0278-0232

Journal Code: GB2
Languages: ENGLISH
Document type: JOURNAL ARTICLE

We have investigated the cytotoxic performance of two different anti-CD7/anti-saporin BsAb's (HB2 x DB7-18 and Q1.1), three anti-CD38/anti-saporin BsAb's (OKT10 x RabSap, OKT10 x DB7-18 and Q4.1) and an anti-CD7 (HB2-Sap) and anti-CD38-saporin (OKT10-Sap) immunotoxin for delivering the ribosome inactivating protein (rip) to the human T-cell acute lymphoblastic leukemia cell line HSB-2. In the case of CD7 as target molecule the immunotoxin outperformed both anti-CD7 BsAb's being six times more effective than HB2 x DB7-18 and 98 times more so than Q1.1 at effectively inhibiting protein synthesis in a dose dependent manner. The chemically constructed HB2 x DB7-18 BsAb was more effective at inhibiting protein synthesis and cell growth in target HSB-2 cells in a dose dependent manner than the quadroma produced BsAb Q1.1. Both BsAb demonstrated a prozone effect used at concentrations above 0.1 nM though this was more pronounced for Q1.1 than for HB2 x DB7-18. The prozone effect was partially though not completely reversed by increasing the concentration of saporin in the system. In the case of CD38 as target molecule the anti-CD38 IT OKT10-Sap performed poorly, never actually achieving its IC50. Two BsAb's constructed with monoclonal anti-saporin Fab **arms** each recognizing a different epitope on the saporin molecule also performed poorly. In contrast the BsAb OKT10 x RabSap constructed with Fab derived from a rabbit polyclonal anti-saporin antiserum performed in a dose dependent manner achieving its IC50 at a concentration of 1.3 nM. This BsAb also exhibited a prozone effect. These results exemplify the importance of cross linking adjacent target molecules on the cell surface in order to achieve effective delivery of saporin to the cell interior.

1/7/14
DIALOG(R)File 155:MEDLINE(R)

08376344 95355152
Engineering high affinity humanized anti-p185HER2/anti-CD3 bispecific F(ab')2 for efficient lysis of p185HER2 overexpressing tumor cells.
Zhu Z; Lewis GD; Carter P
Department of Cell Genetics, Genentech Inc., South San Francisco, CA 94080, USA.
Int J Cancer (UNITED STATES) Jul 28 1995, 62 (3) p319-24, ISSN 0020-7136 Journal Code: GQU
Languages: ENGLISH
Document type: JOURNAL ARTICLE

We previously constructed a humanized anti-p185HER2/anti-CD3 **bispecific antibody** variant, BsF(ab')2 v1 which retargets the cytotoxic activity of human T cells in vitro against human breast tumor cells which overexpress the p185HER2 product of the HER2/neu (c-erbB-2) protooncogene. Subsequently we identified an improved anti-CD3 variant, v9, which binds to T cells with approx. 100-fold higher affinity than the original variant, v1. Here we demonstrate that BsF(ab')2 v9 is more potent than BsF(ab')2 v1 in stimulating the proliferation of both resting peripheral blood lymphocytes (PBL) and IL-2-activated, long-term cultured T lymphocytes (ATL). In addition, at low concentrations (0.01-1 ng/ml) BsF(ab')2 v9 is much more efficient than BsF(ab')2 v1 in directing lysis of p185HER2-overexpressing tumor cells by IL-2 activated PBL. In contrast, at higher concentration BsF(ab')2 v9 and BsF(ab')2 v1 have similar potency in retargeted cytotoxicity. At BsF(ab')2 v9 concentrations of > or = 1 ng/ml the susceptibility of p185HER2-expressing tumor cells to lysis is apparently independent of the level of p185HER2 expression. At lower concentrations of BsF(ab')2 v9 and/or lower ratios of effector to target

cells the extent of lysis is reduced, in some cases improving the selectivity of lysis of high p185HER2 expressors over low expressors. Thus selection of a high affinity anti-CD3 **arm** is likely important in the design of BsF(ab')2 for retargeting the cytotoxicity of T cells to tumors. The dose of BsF(ab')2 v9 in any future clinical evaluation will require optimization to maximize anti-tumor efficacy whilst minimizing potential toxicity against normal tissue expressing p185HER2.

1/7/15
DIALOG(R)File 155:MEDLINE(R)

08159023 95383036
Induction of tumour cell lysis by a **bispecific antibody** recognising epidermal growth factor receptor (EGFR) and CD3.
Knuth A; Bernhard H; Jager E; Wolfel T; Karbach J; Jaggle C; Strittmatter W; Meyer zum Buschenfelde KH
II Medizinische Klinik, Hamatologie/Onkologie, Krankenhaus Nordwest, Frankfurt a. Main, Germany.
Eur J Cancer (ENGLAND) 1994, 30A (8) p1103-7, ISSN 0959-8049
Journal Code: ARV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
A **bispecific antibody** construct (bAb) recognising CD3 and epidermal growth factor receptor (EGFR) was studied in vitro. Human peripheral blood lymphocytes (PBL), pre-activated with monoclonal antibody OKT-3 or with irradiated tumour cells, were **armed** with the bAb construct and targeted to autologous and allogeneic tumour target cells in culture. bAb EGFR x CD3 promoted significant cytolysis even at a concentration of 1 ng/ml. The specificity of target cell lysis was provided by the EGFR specificity of the bAb, as tumour cells negative for EGFR were not lysed. However, not only EGFR-positive tumour cells but also EGFR-positive normal cells were killed. Human renal cancer cell lines and the normal autologous kidney cell cultures expressing the same level of EGFR molecules were lysed to a similar extent. These results may contribute toward the planning of future clinical trials with such bAb.

1/7/16
DIALOG(R)File 155:MEDLINE(R)

07882106 94187754
A bifunctional murine::human chimeric antibody with one antigen-binding **arm** replaced by bacterial beta-lactamase.
De Sutter K; Fiers W
Laboratory of Molecular Biology, Gent University, Belgium.
Mol Immunol (ENGLAND) Mar 1994, 31 (4) p261-7, ISSN 0161-5890
Journal Code: NG1
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We here report the genetic engineering of a murine::human chimeric antibody--directed against the tumor marker human placental alkaline phosphatase--in which one antigen-binding **arm** (Fab) has been replaced by Escherichia coli beta-lactamase (Bla). A mutated Bla gene in which the termination codon had been replaced by GAG, was fused in-phase to the cDNA sequence encoding the hinge region, CH2 and CH3 of the human IgG3 heavy chain. The resulting BlaHG3f fusion gene was placed under control of the Simian Virus 40 late promoter, and transiently expressed in COS-1 cells together with the genes encoding the murine light and murine::human

chimeric heavy chains. Approximately 200 ng/ml of correctly assembled bifunctional antibody-Bla immunoconjugates were detected in the culture supernatant. This observation indicates that Bla (with its own leader peptide) can efficiently direct secretion into the culture medium of adventitious sequences fused at its C-terminus. Furthermore, the assembly in the Fc region was not affected by steric hindrance due to a Bla moiety and an Fab **arm** in close proximity. The antibody-Bla immunoconjugate could be of therapeutic value for the activation of cephalosporin-based anti-cancer prodrugs at the tumor site. Moreover, the expression strategy adopted here is particularly suitable for a quick and convenient analysis of newly designed gene products in which the Bla moiety has been replaced by other enzymes or by antigen-binding fragments in order to engineer **bispecific antibodies**.

1/7/17
DIALOG(R)File 155:MEDLINE(R)

07504302 93177744
The role of apoptosis in antibody-dependent cellular cytotoxicity.
Curnow SJ; Glennie MJ; Stevenson GT
Lymphoma Research Unit, Tenovus Laboratory, General Hospital, Southampton, UK.
Cancer Immunol Immunother (GERMANY) 1993, 36 (3) p149-55, ISSN 0340-7004 Journal Code: CN3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Apoptosis in three lymphoma cell lines has been studied following cytotoxicity induced in vitro by normal human blood lymphocytes utilizing either natural killer (NK) or antibody-dependent cellular cytotoxic (ADCC) mechanisms. Guinea-pig L2C leukaemic lymphocytes, but not the human cell lines Daudi and Jurkat, revealed a degree of time- and temperature-dependent apoptotic death upon simple culture in vitro. NK cytotoxicity at low effector:target ratios (E:T) induced both release of 51Cr and apoptosis. However NK cytotoxicity at higher E:T, and ADCC at all E:T, increased the level of 51Cr release while reducing the level of apoptosis. The findings were consistent with the apoptotic process being cut short by intervention of necrotic death. The same characteristics accompanied ADCC whether the effectors were recruited by Fc gamma regions of antibody coating the targets, or by **bispecific antibodies** attaching one **arm** to the targets and the other to Fc gamma receptors type III on effectors. This finding, and the high level of cytotoxicity elicited by the bispecific method, confirm the belief that NK cells, in addition to exerting NK cytotoxicity, represent the principal effectors for ADCC among blood mononuclear cells. Our results suggest that NK cells have both apoptotic and necrotic mechanisms available for killing their targets, but use only the latter for ADCC.

1/7/18
DIALOG(R)File 155:MEDLINE(R)

07301171 92113462
Development of humanized **bispecific antibodies** reactive with cytotoxic lymphocytes and tumor cells overexpressing the HER2 protooncogene.
Shalaby MR; Shepard HM; Presta L; Rodrigues ML; Beverley PC; Feldmann M; Carter P
Department of Cell Biology, Genentech, Inc., South San Francisco,

California 94080.
J Exp Med (UNITED STATES) Jan 1 1992, 175 (1) p217-25, ISSN 0022-1007 Journal Code: I2V
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The HER2 protooncogene encodes a 185-kD transmembrane phosphoglycoproteins, human epidermal growth factor receptor 2 (p185HER2), whose amplified expression on the cell surface can lead to malignant transformation. Overexpression of HER2/p185HER2 is strongly correlated with progression of human ovarian and breast carcinomas. Recent studies have shown that human T cells can be targeted with **bispecific antibody** to react against human tumor cells in vitro. We have developed a bispecific F(ab')2 antibody molecule consisting of a humanized **arm** with a specificity to p185HER2 linked to another **arm** derived from a murine anti-CD3 monoclonal antibody that we have cloned from UCHT1 hybridoma. The antigen-binding loops for the anti-CD3 were installed in the context of human variable region framework residues, thus forming a fully humanized BsF(ab')2 fragment. Additional variants were produced by replacement of amino acid residues located in light chain complementarity determining region 2 and heavy chain framework region 3 of the humanized anti-CD3 **arm** . Flow cytometry analysis showed that the bispecific F(ab')2 molecules can bind specifically to cells overexpressing p185HER2 and to normal human peripheral blood mononuclear cells bearing the CD3 surface marker. In additional experiments, the presence of bispecific F(ab')2 caused up to fourfold enhancement in the cytotoxic activities of human T cells against tumor cells overexpressing p185HER2 as determined by a 51Cr release assay. These bispecific molecules have a potential use as therapeutic agents for the treatment of cancer.

1/7/19
DIALOG(R)File 155:MEDLINE(R)

07191806 93053063
Engineering a humanized bispecific F(ab')2 fragment for improved binding to T cells.
Rodrigues ML; Shalaby MR; Werther W; Presta L; Carter P
Department of Protein Engineering, Genentech Inc., South San Francisco, CA 94080.
Int J Cancer Suppl (UNITED STATES) 1992, 7 p45-50, ISSN 0020-7136 Journal Code: GRM
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We recently constructed a humanized **bispecific antibody** (BsF(ab')2v1) by separate E. coli expression of each Fab' **arm** followed by directed chemical coupling in vitro. BsF(ab')2 v1 (anti-CD3/anti-p185HER2) was demonstrated to retarget the cytotoxic activity of human CD3+ CTL in vitro against the human breast-tumor cell line, SK-BR-3, which over-expresses the p185HER2 product of the proto-oncogene HER2. Our minimalistic humanization strategy is to install as few murine residues as possible into a human antibody in order to recruit antigen-binding affinity and biological properties comparable to that of the murine parent antibody. This strategy proved very successful for the anti-p185HER2 **arm** of BsF(ab')2 v1. In contrast BsF(ab')2 v1 binds to T cells via its anti-CD3 **arm** much less efficiently than does the chimeric BsF(ab')2 which contains the variable domains of the murine parent anti-CD3 antibody. Here we have constructed additional BsF(ab')2 fragments containing variant anti-CD3 **arms** with selected amino acid replacements in an attempt to improve antibody binding to T cells. One such variant, BsF(ab')2 v9, was created by replacing 6 residues in the second

hypervariable loop of the anti-CD3 heavy chain variable domain of BsF(ab')2 v1 with their counterparts from the murine parent anti-CD3 antibody. BsF(ab')2 v9 binds to T cells (Jurkat) much more efficiently than does BsF(ab')2 v1 and almost as efficiently as the chimeric BsF(ab')2. This improvement in the efficiency of T-cell binding of the humanized BsF(ab')2 is an important step in its development as a potential therapeutic agent for the treatment of p185HER2 over-expressing cancers.

1/7/20
DIALOG(R)File 155:MEDLINE(R)

07000719 91369817
Characteristics and performance of a bispecific F (ab'gamma)2 antibody for delivering saporin to a CD7+ human acute T-cell leukaemia cell line.
Flavell DJ; Cooper S; Morland B; Flavell SU
University Department of Pathology, Southampton General Hospital, UK.
Br J Cancer (ENGLAND) Aug 1991, 64 (2) p274-80, ISSN 0007-0920
Journal Code: AV4
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have investigated the efficacy of a F(ab'gamma)2 **bispecific antibody** (BsAb) with dual specificity for the CD7 molecule in one Fab **arm** and for the ribosome inactivating protein (rip) saporin in the other **arm**, for delivering saporin to the acute T-cell leukaemia cell line HSB-2. Saporin titration experiments revealed that BsAb increased the toxicity of saporin 435-fold for HSB-2 cells, reducing the IC50 for saporin alone from 0.1 mumol to 0.23 nmol when BsAb was included. The rate of protein synthesis inactivation brought about by BsAb-mediated toxin delivery to HSB-2 cells was very similar to that described for conventional immunotoxins (IT's) with a t10 (time taken for a one log inhibition of protein synthesis compared with controls) of 46 h obtained at a saporin concentration of 1 nmol and 226 h at 0.1 nmol. BsAb titration studies demonstrated a clear dose response effect of BsAb concentration on target cell protein synthesis inhibition and cell proliferation. The absolute specificity of toxin delivery was unequivocally demonstrated by a failure of BsAb to deliver an effective dose of saporin to the CD7- cell line HL60 and by the blocking of BsAb-mediated delivery of saporin to HSB-2 cells with an excess of F(ab)2 fragments of the anti-CD7 antibody, HB2. These studies have clearly demonstrated the effectiveness of this BsAb for delivering saporin to a T-ALL cell line utilising CD7 as the target molecule on the cell surface. BsAb's would therefore appear to offer a realistic alternative to IT's for toxin delivery to tumour cells and may even offer certain advantages over conventional IT's for clinical use.

1/7/21
DIALOG(R)File 155:MEDLINE(R)

06966439 91268582
Trispecific F(ab')3 derivatives that use cooperative signaling via the TCR/CD3 complex and CD2 to activate and redirect resting cytotoxic T cells.
Tutt A; Stevenson GT; Glennie MJ
Tenovus Research Laboratory, General Hospital, Southampton, United Kingdom.
J Immunol (UNITED STATES) Jul 1 1991, 147 (1) p60-9, ISSN 0022-1767
Journal Code: IFB
Languages: ENGLISH
Document type: JOURNAL ARTICLE

To investigate whether the retargeting of resting CTL can benefit from cooperative signaling between the TCR/CD3 complex and various accessory molecules, such as CD2, CD4, CD5, and CD8, we have constructed a series of trispecific F(ab')3 derivatives. Each derivative was designed to engage effector T lymphocytes with two Fab' **arms**, and tumor cells with a single Fab' **arm**. They were constructed by selective coupling of three mAb Fab' fragments, primarily via their hinge-region sulfhydryl groups, using the cross-linker o-phenylenedimaleimide. En route to the production of trispecific F(ab')3 antibodies a range of bispecific F(ab')2 derivatives was first prepared which could bind simultaneously to two different receptor molecules on T cells. Bispecific derivatives containing specificities for (CD2 (T11(1)) x CD3), (CD3 x CD4), (CD3 x CD8) or two epitopes on CD2, ((T11(1) x (T11(3)), all yielded two to three times the uptake of [3H]thymidine with fresh PBMC to that seen with intact IgG from anti-CD3 (OKT3). The exception to these findings was a bispecific F(ab')2 derivative with specificities for (CD3 x CD5) which caused slightly less proliferation than the control reagent, OKT3 IgG. When these **bispecific antibodies** were converted into trispecific antibodies (TsAb) by the addition of a Fab' from anti-CD37 they were then all able to retarget resting, unprimed, T cells from fresh PBMC for lysis of CD37+ tumor cells. However, the cytotoxic activity of these reagents fell into two distinct groups: group one, containing (anti-CD3 x anti-CD4 x anti-CD37), (anti-CD3 x anti-CD5 x anti-CD37), and (anti-CD3 x anti-CD8 x anti-CD37), gave minimal lysis and behaved in a similar way to the BsAb, (anti-CD3 x anti-CD37), i.e., no evidence of cooperative signaling for lysis; and group two, containing (anti-T11(1) x anti-CD3 x anti-CD37) and (anti-T11(1) x anti-T11(3) x anti-CD37), which were highly cytotoxic and gave up to 80% specific 51Cr-release. The failure of group one TsAb, in particular (anti-CD3 x anti-CD8 x anti-CD37) which should recruit CD8+ CTL, to give efficient lysis despite having anti-T cell **arms** that were mitogenic as a **bispecific antibody** , indicates that the cooperative signaling for proliferation is probably distinct from the signal(s) provided by group two TsAb that activate for both proliferation and lysis.(ABSTRACT TRUNCATED AT 400 WORDS)

1/7/22
DIALOG(R)File 155:MEDLINE(R)

7/12

05790808 89310366
Triggering T cells by otherwise inert hybrid anti-CD3/antitumor antibodies requires encounter with the specific target cell.
Roosnek E; Lanzavecchia A
Basel Institute for Immunology, Switzerland.
J Exp Med (UNITED STATES) Jul 1 1989, 170 (1) p297-302, ISSN 0022-1007 Journal Code: I2V
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We used a purified **bispecific antibody** (Ab) against CD3 and an ovarian carcinoma (OVCA) antigen to ask whether the binding of a monovalent ligand to CD3 can induce triggering of T cells. In the presence of OVCA cells, this Ab bridges the CD3 complex to the target cell and triggers proliferation and cytotoxicity in T cells. In the absence of target cells; however, this monovalent Ab, even when bound to T cells at high levels, fails to induce any increase in cytosolic Ca2+, nor does it induce responsiveness to IL-2 or modulation of the CD3 complex. Because it is inert when bound monovalently, this hybrid Ab can be used to **arm** in vitro CTL clones, which then retain the capacity to kill the specific tumor for up to 2 d.
? s tumor? and ex(w)vivo

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          452546  TUMOR?
           12404  EX
          242574  VIVO
            8021  EX(W)VIVO
      S2    1195  TUMOR? AND EX(W)VIVO
? s s2 and antibod?

            1195  S2
          516748  ANTIBOD?
      S3     227  S2 AND ANTIBOD?
? s s3 and (antibod?(p)ex)

             227  S3
               0  ANTIBOD?(P)EX
      S4       0  S3 AND (ANTIBOD?(P)EX)
? s s3 not py>1996

             227  S3
          932630  PY>1996
      S5     164  S3 NOT PY>1996
? t s5/3/1-5


 5/3/1
DIALOG(R)File 155:MEDLINE(R)
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09814147   99035083
  Dynamic expression changes in vivo of adhesion and costimulatory
molecules determine load and pattern of lymphoma liver metastasis.
  Rocha M; Kruger A; Umansky V; von Hoegen P; Naor D; Schirrmacher V
  Tumor Immunology Program, Division of Cellular Immunology, German Cancer
Research Center, Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany.
  Clin Cancer Res (UNITED STATES) May 1996, 2 (5) p811-20, ISSN
1078-0432   Journal Code: C2H
  Languages: ENGLISH
  Document type: JOURNAL ARTICLE


 5/3/2
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1999 Dialog Corporation. All rts. reserv.

09253643   97123122
  Pharmacological profile of SB 203580, a selective inhibitor of cytokine
suppressive binding protein/p38 kinase, in animal models of arthritis, bone
resorption, endotoxin shock and immune function.
  Badger AM; Bradbeer JN; Votta B; Lee JC; Adams JL; Griswold DE
  Department of Cellular Biochemistry, SmithKline Beecham Pharmaceuticals,
King of Prussia, Pennsylvania, USA.
  J Pharmacol Exp Ther (UNITED STATES) Dec 1996, 279 (3) p1453-61,
ISSN 0022-3565   Journal Code: JP3
  Languages: ENGLISH
  Document type: JOURNAL ARTICLE


 5/3/3
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1999 Dialog Corporation. All rts. reserv.
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09225230 96139468
Immunochemical characterization and transacting properties of upstream stimulatory factor isoforms.
Viollet B; Lefrancois-Martinez AM; Henrion A; Kahn A; Raymondjean M; Martinez A
Institut Cochin de Genetique Moleculaire, U129 INSERM, Universite Rene Descartes, Paris, France.
J Biol Chem (UNITED STATES) Jan 19 1996, 271 (3) p1405-15, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: JOURNAL ARTICLE

5/3/4
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1999 Dialog Corporation. All rts. reserv.

09055661 97182973
Comparative preclinical study of three bone marrow purging methods using PCR evaluation of residual t(14;18) lymphoma cells.
Yerly-Motta V; Racadot E; Fest T; Bastard C; Ferrand C; Deschaseaux ML; Herve P
Etablissement de Transfusion Sanguine de Franche-Comte, Besancon, France.
Leuk Lymphoma (SWITZERLAND) Oct 1996, 23 (3-4) p313-21, ISSN 1042-8194 Journal Code: BNQ
Languages: ENGLISH
Document type: JOURNAL ARTICLE

5/3/5
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1999 Dialog Corporation. All rts. reserv.

08990651 97194766
Immunophenotypic characterization of human primary and metastatic melanoma infiltrating leukocytes.
Bodey B; Bodey B Jr; Siegel SE; Luck JV; Kaiser HE
Department of Pathology, School of Medicine, University of Southern California, Los Angeles 90033, USA.
Anticancer Res (GREECE) Nov-Dec 1996, 16 (6B) p3439-46, ISSN 0250-7005 Journal Code: 59L
Languages: ENGLISH
Document type: JOURNAL ARTICLE
? s s5 and tumor?(w)cell

164 S5
452546 TUMOR?
1287239 CELL
19114 TUMOR?(W)CELL
S6 22 S5 AND TUMOR?(W)CELL
? t s6/7/1-22

6/7/1
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1999 Dialog Corporation. All rts. reserv.

09814147 99035083
Dynamic expression changes in vivo of adhesion and costimulatory molecules determine load and pattern of lymphoma liver metastasis.
Rocha M; Kruger A; Umansky V; von Hoegen P; Naor D; Schirrmacher V

Tumor Immunology Program, Division of Cellular Immunology, German Cancer Research Center, Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany.
Clin Cancer Res (UNITED STATES) May 1996, 2 (5) p811-20, ISSN 1078-0432 Journal Code: C2H
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Although intradermal primary **tumor** growth and spontaneous liver metastasis of ESbL-lacZ lymphoma in syngeneic DBA/2 mice are progressive and malignant, they are characterized by a transient plateau period with a constant **tumor** diameter and a low number of metastasized cells in the liver. This period, which was shown to be immune dependent, was followed by a second expansion phase characterized by a preferential localization of **tumor** cells in the periportal areas of liver lobules (mosaic phenotype). To elucidate possible mechanisms leading to the plateau period as well as for the mosaic-like metastasis pattern, we investigated, using flow cytometry analysis, alterations in costimulatory and adhesion molecule expression in liver sinusoidal cells as well as in **tumor** cells isolated directly **ex vivo** throughout the kinetics of metastasis. In **tumor** and sinusoidal cells, we found up-regulation in the expression of MHC class II and B7 molecules during the plateau period. These molecules, which facilitate cell-mediated immune responses, were again down-regulated during the final exponential **tumor** growth and metastasis. In the final expansion phase, in which the mosaic phenotype of liver metastasis is seen, we detected a significant increase of leukocyte function-associated antigen-1/intercellular adhesion molecule-1 expression in both **tumor** and sinusoidal cells, suggesting **tumor cell** -sinusoidal cell interactions. vascular cell adhesion molecule-1/very late activated antigen-4 did not show any modification during the whole metastatic process. In vivo application of monoclonal **antibodies** directed to leukocyte function-associated antigen-1 and intercellular adhesion molecule-1 appeared to block the spread of metastasis, while no effect was seen with monoclonal **antibodies** directed to vascular cell adhesion molecule-1 and very late activated antigen-4. This study reveals in situ expression changes of cell surface molecules in **tumor** and host cells during metastasis. The changes seen during the plateau phase and during the second expansion phase differ, suggesting associations with mechanisms of immune control and **tumor** immune evasion, respectively.

6/7/2
DIALOG(R)File 155:MEDLINE(R)

09055661 97182973
Comparative preclinical study of three bone marrow purging methods using PCR evaluation of residual t(14;18) lymphoma cells.
Yerly-Motta V; Racadot E; Fest T; Bastard C; Ferrand C; Deschaseaux ML; Herve P
Etablissement de Transfusion Sanguine de Franche-Comte, Besancon, France.
Leuk Lymphoma (SWITZERLAND) Oct 1996, 23 (3-4) p313-21, ISSN 1042-8194 Journal Code: BNQ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The t(14;18) chromosomal translocation occurring in most follicular lymphomas can be exploited by a Bcl2/JH polymerase chain reaction (PCR) to detect residual disease and to monitor the effectiveness of **ex-vivo tumor cell** immunological purging. We first demonstrated the 10(-5) Bcl2/JH PCR sensitivity with serial dilutions of OCY-LY8 lymphoma cell lines in normal mononuclear cells; and then the specificity and reproductibility of this technique by analysing follicular and non follicular lymphoma samples. With the Bcl2/JH PCR, we tested the

efficiency of three marrow purging protocols with an experimentally contaminated bone marrow either treated by three anti-B cell monoclonal **antibodies** (mAb) followed by three rounds of rabbit complement or two rounds of immunomagnetics beads. Samples obtained after each purging were amplified by Bcl2/JH PCR and hybridized with PFL3 probe. We were able to produce a 2 to 3 log **tumor cell** reduction after three rounds of complement and a 4 to 5 log reduction after two rounds of beads. This study showed that it is feasible to use the Bcl2/JH PCR technique for residual cell lymphoma detection in patients undergoing intensive chemotherapy or BM transplantation. These results indicate that **ex-vivo** immunomagnetic BM purging is probably superior to complement mediated lysis for the eradication of B lymphoma cells from the marrow of patients undergoing autologous transplantation.

6/7/3
DIALOG(R)File 155:MEDLINE(R)

08909510 97122505

CD3-CD28 costimulation as a means to avoiding T cell preactivation in bispecific monoclonal **antibody**-based treatment of ovarian carcinoma.

Mazzoni A; Mezzanzanica D; Jung G; Wolf H; Colnaghi MI; Canevari S
Division of Experimental Oncology E, Istituto Nazionale Tumori, Milan, Italy.

Cancer Res (UNITED STATES) Dec 1 1996, 56 (23) p5443-9, ISSN 0008-5472 Journal Code: CNF
Languages: ENGLISH
Document type: JOURNAL ARTICLE

One of the major limitations to the immunotherapy of ovarian carcinoma based on the use of anti-CD3/antitumor bispecific monoclonal **antibodies** (bi-mAb) is the need for preactivation of effector cells **ex vivo**, because cross-linking of the T cell receptor-CD3 complex per se may lead to T-cell unresponsiveness or even apoptosis. The bi-mAb OC/TR, which recognizes the folate-binding protein (FBP) overexpressed in 90% of ovarian carcinomas and the CD3 molecule on T cells, has demonstrated efficacy in a clinical setting. Here we investigated the possibility of delivering accessory signals to OC/TR-retargeted peripheral blood mononuclear cells (PBMCs) via an anti-CD28 mAb or an anti-FBP/anti-CD28 bi-mAb. Coculture of resting PBMCs from healthy donors with OC/TR, anti-FBP/anti-CD28 bi-mAb, and FBP+ **tumor cell** lines resulted in a highly activated phenotype of effector cells and in a dramatic in vitro growth inhibition of the target cells without an increase in OC/TR-redirected lysis. Whereas both the CD4 and CD8 T cell subsets were involved in the growth inhibition, only the CD8 subpopulation accounted for the cytotoxic activity. The in vitro **tumor** growth inhibition was mediated mainly by soluble factors, which were active on both FBP+ and FBP- ("bystander effect") cell lines. Activation and antitumor activity were also observed, albeit to a lesser extent, using OC/TR and monospecific bivalent anti-CD28 mAb. In vitro analysis demonstrated that cross-linking between **tumor** and effector cells for at least 24 h was needed to achieve T-cell activation and development of antitumor activities. Thus, **ex vivo** CD3-CD28 costimulation on resting PBMCs might be of therapeutic utility for local treatment of minimal residual disease.

6/7/4
DIALOG(R)File 155:MEDLINE(R)

08868584 97109082

Transplantation of CD34+ hematopoietic progenitor cells [see comments]
Berenson RJ; Shpall EJ; Auditore-Hargreaves K; Heimfeld S; Jacobs C; Krieger MS
CellPro, Inc., Bothell, Washington, USA.
Cancer Invest (UNITED STATES) 1996, 14 (6) p589-96, ISSN 0735-7907 Journal Code: CAI
Comment in Cancer Invest 1996;14(6):640-1
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW LITERATURE

We have developed an avidin-biotin immunoadsorption technique in conjunction with a monoclonal anti-CD34 **antibody** that is capable of selecting CD34+ progenitor cells from marrow and mobilized peripheral blood. Clinical studies with these CD34+ selected cells have shown that the cells are capable of rapid and durable engraftment. In addition, there is significantly less infusional toxicity to the patient because the volume in which the CD34+ selected cells are contained is much less than that of a typical marrow or apheresis buffy coat. Selection of CD34+ progenitor cells also offers other potential advantages, including T-cell depletion of allografts and **tumor cell** depletion of autografts. CD34+ selection can also be used to facilitate other manipulations of marrow and peripheral blood, including gene transfection, **ex vivo** stem cell expansion, **tumor** purging, and progenitor cell banking. Future graft engineering studies are expected to clarify these relationships and enable refinement of the graft to the point at which GVHD can be minimized, graft survival maximized, and relapse-free survival prolonged. (79 Refs.)

6/7/5
DIALOG(R)File 155:MEDLINE(R)

08825907 96389941
The effect of high dose vitamin A on the morphology and proliferative activity of xenograft lung and head and neck cancer.
Mourad WA; Bruner JM; Vallieres E; McName C; Alabdulwahed S; Scott K; Oldring DJ
Department of Pathology, University of Alberta, Edmonton, Canada.
In Vivo (GREECE) May-Jun 1996, 10 (3) p329-33, ISSN 0258-851X Journal Code: A6F
Languages: ENGLISH
Document type: JOURNAL ARTICLE

In vitro studies have suggested that vitamin A lowers invasive potential of squamous cell carcinoma. Epidemiological data have also indicated that high dose vitamin A may improve survival in patients with previously resected lung carcinoma. To our knowledge, no studies have attempted to test the in vivo effect of vitamin A on the morphology and growth rate of lung and head and neck cancer. Freshly resected **tumor cell** suspensions were obtained by **ex vivo** fine needle aspiration and injected subcutaneously in duplicate in athymic male nude mice. Two to six weeks post-engraftment tests and controls were separated for each xenograft. Mice with test xenografts were given water soluble vitamin A (Aquasol ATM, Astra pharmaceutical, Westborough, MA, U.S.A) at a dose of 10,000 U/Kg/day intraperitoneally for 6 to 10 weeks (median 8 weeks). One to two hours prior to sacrifice bromodexouridine (BrdU) was injected intraperitoneally to assess the S-phase fraction in both test and control xenografts. Blood vitamin A levels in test and control animals were measured after sacrifice using high performance liquid chromatography (HPLC). Sections of test and control xenografts were routinely stained to assess morphologic differentiation and mitotic counts. Unstained sections of xenografts were immunostained by the **antibody** to BrdU to test for BrdU labeling index (BLI) reflecting S-phase fraction (SPF) and also by the

MIB-1 **antibody** to assess proliferative activity. Eighteen **tumors** were studied. These included 9 squamous cell carcinomas of the lung, 5 squamous cell carcinomas of the head and neck, and 4 adenocarcinomas of the lung. Blood levels of vitamin A in test animals were 7 to 23 times those of the control animals (median 13 times). Neovascularization of the xenografts was seen in all cases. The morphology and mitotic activity of the test and control xenografts showed no significant difference. SPF and proliferative activity measured by BrdU and MIB-1 immunolabelling respectively showed no significant difference between test and control xenografts. Our study suggests that there is no significant in vivo effect of high dose vitamin A on the morphology and growth rate of xenografted non small cell carcinoma of the lung or squamous cell carcinoma of the head and neck.

6/7/6
DIALOG(R)File 155:MEDLINE(R)

08663188 96163526
Pulmonary metastases neutralization and **tumor** rejection by in vivo administration of beta glucan and bispecific **antibody**.
7/12
Penna C; Dean PA; Nelson H
Department of Surgery, Mayo Clinic, Rochester, MN 55905, USA.
Int J Cancer (UNITED STATES) Jan 26 1996, 65 (3) p377-82, ISSN 0020-7136 Journal Code: GQU
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Bispecific **antibody** (BsAb) with specificity for **tumor cell** surface antigen and the CD3 molecule on T cells can redirect activated T cells to lyse **tumor** cells. Since the **ex vivo** expansion and activation of T cells is impractical and ineffective for treating established **tumors**, we tested whether the immune stimulant beta glucan could in situ-activate T cells, which could secondarily be retargeted with BsAbs to lyse **tumor** cells. To test for **tumor** neutralization, C3H/HeN mice were injected i.v. with Cl-62 melanoma cells and immediately treated with i.p. beta glucan and/or anti-CD3 (500A2) x anti-p97 (96.5) F(ab')2 BsAb i.v. Pulmonary metastases were counted 14 days later. To test for **tumor** rejection and survival in a solid **tumor** model, mice were injected s.c. and i.p. with Cl-62 cells and 7 days later administered beta glucan i.p. and/or F(ab')2 BsAb i.v. In the neutralization model, there was a significant reduction in the number of metastases in the beta glucan + BsAb group, as compared with controls, and with beta glucan alone. In the established **tumor** model, beta glucan + BsAb reduced the incidence of s.c. **tumors** as compared with control, with BsAb alone and with beta glucan alone. It also prolonged survival of **tumor** -bearing mice compared with control, BsAb alone and beta glucan alone. We conclude that T cells can be activated in vivo by beta glucan and retargeted with F(ab')2 BsAb.

6/7/7
DIALOG(R)File 155:MEDLINE(R)

08013600 95006297
A combination of anti-CD15 monoclonal **antibody** PM-81 and 4-hydroperoxycyclophosphamide augments **tumor** cytotoxicity while sparing normal progenitor cells.
Rubin J; Malley V; Ball ED
Department of Medicine, University of Pittsburgh Medical Center, PA

15213.
J Hematother (UNITED STATES) Summer 1994, 3 (2) p121-7, ISSN 1061-6128 Journal Code: B3T
Languages: ENGLISH
Document type: JOURNAL ARTICLE
A cyclophosphamide congener, 4-hydroperoxycyclophosphamide (4HC), has been used to purge bone marrow (BM) of residual leukemia cells **ex vivo** for use in support of high-dose chemotherapy for patients with acute myeloid leukemia (AML) undergoing autologous BM transplantation (ABMT). The efficacy and toxicity of 4HC are dose-related. The maximally tolerated concentration, 60-100 micrograms/ml, is toxic to **tumor** cells but also to normal committed hematopoietic progenitor cells. The anti-CD15 monoclonal **antibody** (mAb) PM-81 has also been employed for purging BM in patients with AML. In some patients, all **tumor** cells may not be lysed due to antigenic heterogeneity. Because the two agents used individually are associated with potential limitations in terms of toxicity to normal cells and efficacy of **tumor cell** purging, using these agents together might have advantages. In fact, in this study the use of these two agents together in subtherapeutic concentration ranges as single agents revealed killing of cells from the HL60 and NB4 promyelocytic leukemia cell lines in addition to cells from patients with AML while sparing normal progenitor cells. Surprisingly, not only did the combination enhance killing of **tumor** cells, but the order of addition of the two agents was important in maximizing toxicity to **tumor** cells. Adding mAb+complement (C') first or simultaneously to 4HC was less effective than adding 4HC first followed by mAb + C'. This combination regimen was toxic to HL60 and NB4 leukemia cells that may not be killed by the mAb alone due to antigen-negative **tumor** cells or by low concentrations of 4HC.(ABSTRACT TRUNCATED AT 250 WORDS)

6/7/8
DIALOG(R)File 155:MEDLINE(R)

07453556 93200753
Bone marrow purging prior to autologous transplantation.
Zingsem J; Stahlhut K; Serke S; Zeiler T; Weisbach V; Zimmermann R; Siegert W; Eckstein R
Abteilung fur Transfusionsmedizin, Universitatsklinik Erlangen, Erlangen-Nurnberg, BRD.
Infusionsther Transfusionsmed (SWITZERLAND) Dec 1992, 19 (6) p288-90, ISSN 1011-6966 Journal Code: BIW
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Our data suggest that **ex vivo** bone marrow purging using monoclonal **antibodies** (MoAbs) and sheep-anti-mouse immunobeads (SAM beads) prior to autologous bone marrow transplantation (ABMT) allows satisfactory **tumor cell** reduction without critical stem cell losses. Nevertheless, there is only a reduction but no elimination of **tumor** cells. The consequences will have to be clinically discussed.

6/7/9
DIALOG(R)File 155:MEDLINE(R)

07316173 95086836
Quantitation of **tumor cell** removal from bone marrow: a preclinical model.
Moss TJ; Xu ZJ; Mansour VH; Hardwick A; Kulcinski D; Ishizawa L; Law P;

Gee A
Cedars-Sinai Medical Center, Ahmanson Pediatric Center, Los Angeles, CA 90048.
J Hematother (UNITED STATES) Spring 1992, 1 (1) p65-73, ISSN 1061-6128 Journal Code: B3T
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have developed a multiassay system consisting of fluorescence microscopy, immunocytology and **tumor** colony assay to monitor the removal of **tumor** cells from bone marrow. This system was tested in preclinical purging experiments in which neuroblastoma cells were seeded into bovine marrow and purged by treatment with monoclonal **antibodies** and immunomagnetic beads. Eight experiments were performed on two different neuroblastoma cell lines seeded at 2% and/or 5% contamination. We consistently demonstrated greater than a 3 log removal with one cycle of **antibody**/bead treatment and greater than a 1 log further reduction by addition of a second cycle. We also demonstrated removal of all detectable **tumor** stem cells by this purging method. We feel that this system will prove valuable for monitoring **ex vivo tumor** removal in future clinical studies and should be considered for use in other purging trials.

6/7/10
DIALOG(R)File 155:MEDLINE(R)

07166270 93014360
HLA-B5-restricted auto-**tumor**-specific cytotoxic T cells generated in mixed lymphocyte-**tumor-cell** culture.
Wang P; Vegh Zs; Vanky F; Klein E
Department of Tumor Biology, Karolinska Institute, Stockholm, Sweden.
Int J Cancer (UNITED STATES) Oct 21 1992, 52 (4) p517-22, ISSN 0020-7136 Journal Code: GQU
Languages: ENGLISH
Document type: JOURNAL ARTICLE
T-cell-enriched lymphocyte populations derived from the malignant exudate of a patient with ovarian carcinoma were exposed to autologous **tumor** cells in the mixed lymphocyte-**tumor-cell** culture (MLTC) and propagated for 42 days. Proliferation of lymphocytes depended on exposures to autologous **tumor** cells and on the presence of IL-2. After 7 days, the MLTC-lymphocytes lysed K562 and the autologous **tumor** cells. The latter effect was not inhibited by monoclonal **antibodies** (MAbs) reactive with MHC class-I antigens or with CD3. After 7 restimulations, the culture was enriched in CD8+ cells (92%) and showed selective lytic activity against the autologous **tumor**. This function was inhibited by the alpha-class I or alpha-CD3 MAbs, and also by **antibodies** reactive with the HLA B locus or B5 allele products. The **antibodies** reactive with HLA A molecules had no such effect. It seems therefore that the function of the CTLs was restricted by HLA B5. Analysis of the TCR beta genes indicated clonal T-cell expansion in this culture. This MLTC was 1 of 21 initiated with 11 blood- and 10 **tumor**-derived lymphocyte (TIL) populations prepared from the malignant effusions of ovarian carcinoma patients. None of these **ex-vivo** lymphocytes lysed autologous **tumor** cells. In 17 MLTCs the lymphocytes did not proliferate, and in 3 cultures the proliferation was maintained only for 2-3 weeks. In 3 of 4 cultures auto-**tumor** cytotoxicity was induced.

6/7/11
DIALOG(R)File 155:MEDLINE(R)

07155262 92348065
MHC class-I-restricted auto-**tumor**-specific CD4+CD8- T-cell clones established from autologous mixed lymphocyte-**tumor**-**cell** culture (MLTC).
Wang P; Vanky F; Klein E
Department of Tumor Biology, Karolinska Institute, Stockholm, Sweden.
Int J Cancer (UNITED STATES) Jul 30 1992, 51 (6) p962-7, ISSN 0020-7136 Journal Code: GQU
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Autologous mixed lymphocyte-**tumor cell** cultures (MLTC) were initiated with cytokine (IFN gamma and TNF alpha)-treated **ex-vivo tumor** cells of lung, ovarian, breast and stomach carcinomas. The cytokine-treated **tumors** expressed class-I but not class-II molecules. Although the proportion of CD8+ lymphocytes increased in the bulk culture of MLTCs, in 5/7 experiments the majority of the established T-cell clones were CD4+. Among the CD8+ clones a high proportion (77%) was cytotoxic, while the proliferative response was more frequent among the CD4+ clones (70%). In 4/26 cytotoxic T-lymphocyte (CTL) clones (3/17 CD4+ and 1/9 CD8+), derived from a patient with class I+ class II- stomach carcinoma, lysis was restricted to the autologous **tumor** cells. These auto-**tumor**-specific clones did not lyse the autologous ConA blasts, the 5 allogeneic **ex-vivo tumors** , the NK-sensitive K562 or the relatively sensitive Daudi cells. The cytotoxicity of these clones was inhibited by pre-incubation of the **tumor** cells with W6/32 (alpha-class I) MAb, or by preincubation of the lymphocytes with OKT3 (alpha-CD3) MAb. The alpha-CD4 (OKT4) MAb had only a marginal effect on the CD4+ clones, while the lytic function of the CD8+ clone was inhibited by the alpha-CD8 (OKT8) MAb. The 3 CD4+ CTL clones also responded with proliferation to the autologous **tumor** cells. This proliferative response was inhibited by the presence of W6/32 MAb. Our results indicate that the auto-**tumor** lysis exerted by CD4+ CTL clones was restricted by the class-I antigens, and that the CD4 molecules of the clones were not essential for the lytic interaction.

6/7/12

07019095 92147681
Isolation and characterization of a novel receptor-type protein tyrosine kinase (hek) from a human pre-B cell line.
Boyd AW; Ward LD; Wicks IP; Simpson RJ; Salvaris E; Wilks A; Welch K; Loudovaris M; Rockman S; Busmanis I
Lions Clinical Cancer Research Laboratory, Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, Victoria, Australia.
J Biol Chem (UNITED STATES) Feb 15 1992, 267 (5) p3262-7, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In this report we describe the identification and characterization of a novel **tumor** -associated receptor-type tyrosine kinase (hek). We produced a monoclonal **antibody** (III.A4) that detected a novel glycoprotein on the immunizing pre-B cell acute lymphoblastic leukemia cell line (LK63). This antigen was shown to be expressed sporadically on hemopoietic **tumor cell** lines and on **ex vivo tumors**. However, using **antibody** staining, the molecule was

undetectable on normal tissues. Further biochemical characterization showed this molecule (hek) to be a phosphoroprotein. This observation taken together with the **tumor**-associated nature of hek expression suggested that hek might be a receptor-type protein tyrosine kinase. This was demonstrated by affinity purification of hek. In in vitro kinase experiments the purified hek protein was autophosphorylated on tyrosine and also mediated tyrosine phosphorylation of casein. Purified hek was subjected to N-terminal amino acid sequence analysis which showed that hek had a unique N terminus. Amino acid sequence determination of peptides from a V8 protease digest of hek yielded one 21-amino acid stretch of sequence which showed close homology with the eph subfamily of protein tyrosine kinases. These studies show hek to be a novel human **tumor**-associated protein tyrosine kinase, which by analogy with previously characterized protein tyrosine kinase proto-oncogenes, may have a role in **tumorigenesis**.

6/7/13
DIALOG(R)File 155:MEDLINE(R)

✓ 7/12

06970221 92003727
Requirement of MHC class I antigen expression on human **tumors** for in vitro recognition by autologous blood lymphocytes.
Vanky F; Klein E
Department of Tumor Biology, Karolinska Institute, Stockholm, Sweden.
Semin Cancer Biol (UNITED STATES) Feb 1991, 2 (1) p55-62, ISSN 1044-579X Journal Code: A6Y
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Expression of class I antigens on **ex-vivo tumor** cells was found to be required for their recognition by autologous blood lymphocytes in vitro. Lymphocyte stimulation (auto-**tumor** stimulation ATS) in mixed lymphocyte **tumor cell** cultures (MLTC) and cytolysis in short term assays (autologous lymphocyte-mediated cytotoxicity ALC) were positive with cells of a proportion of sarcoma and carcinoma patients. In addition to the class I antigens, these **tumors** also carried the adhesion molecule ICAM-1. Monoclonal **antibodies** (MAb) to the MHC class I, but not to class II antigens inhibited lymphocyte proliferation in the MLTC and lysis of **tumor** cells in the ALC tests. In a proportion of originally negative or low expressor **tumors**, in vitro treatment with Interferon gamma and **tumor** necrosis factor alpha induced the expression of class I antigens and/or ICAM-1. In the MLTC the cytokine treated **tumor** cells stimulated the blood lymphocytes and generated cytotoxic effectors which reacted also with the untreated **tumor** cells.

6/7/14
DIALOG(R)File 155:MEDLINE(R)

06828067 92049579
Immunologic purging of marrow assessed by PCR before autologous bone marrow transplantation for B-cell lymphoma [see comments]
Gribben JG; Freedman AS; Neuberg D; Roy DC; Blake KW; Woo SD; Grossbard ML; Rabinowe SN; Coral F; Freeman GJ; et al
Division of Tumor Immunology, Dana-Farber Cancer Institute, Boston, MA 02115.
N Engl J Med (UNITED STATES) Nov 28 1991, 325 (22) p1525-33, ISSN 0028-4793 Journal Code: NOW

tumor cells decreases the probability of infusing **tumorigenic** cells with the ABMT. There is considerable experience in **tumor** detection and purging for neuroblastoma, but little has been done for other childhood solid **tumors** . Future investigations of ABMT will aim to further increase disease-free survival by intensifying induction and marrow-ablative regimens and by developing therapies to be given after ABMT that are directed at minimal residual disease. As pilot investigations mature, the efficacy of ABMT and conventional chemotherapy will be compared in multi-institution randomized studies. (183 Refs.)

6/7/16
DIALOG(R)File 155:MEDLINE(R)

06674268 91120971
Use of the polymerase chain reaction to monitor the effectiveness of **ex vivo tumor cell** purging.
Negrin RS; Kiem HP; Schmidt-Wolf IG; Blume KG; Cleary ML
Division of Hematology, Stanford University Medical Center, CA 94305.
Blood (UNITED STATES) Feb 1 1991, 77 (3) p654-60, ISSN 0006-4971 Journal Code: A8G
Contract/Grant No.: 1PO1-CA 49605, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The polymerase chain reaction (PCR) was used to detect residual malignant disease before and after **ex vivo** purging with monoclonal **antibodies** and complement or immunomagnetic treatment of BM samples contaminated with known numbers of t(14;18)-carrying **tumor** cells. Sensitivity of the PCR was demonstrated by detecting a specific t(14;18) amplification product in DNA extracted from a preparation consisting of one **tumor cell** among 10(5) normal cells. When BM contaminated with 1% to 5% t(14;18)-carrying cells from the B-cell lymphoma line SU-DHL-4 was subjected to two rounds of anti-B-cell pool of **antibodies** and complement (Ab-C) treatment a 3- to 4-log reduction of the pretreatment PCR signal was observed. A similar log-cell kill was detected using an independent clonogenic assay confirming the utility of the PCR approach. BM contaminated with a second B-cell lymphoma cell line, OCI-Ly8, was more resistant because a third cycle of Ab-C treatment was required to obtain a similar reduction in the PCR signal. A similar 4 logs of **tumor cell** removal was obtained using anti-B-cell **antibodies** conjugated to magnetic beads. These studies demonstrate that the t(14;18) PCR can be used to detect levels of **tumor** cells as low as 0.001%. This approach can be used to determine the effectiveness of BM purging in patients undergoing autologous BM transplantation as well as to assess the biologic role of minimal marrow disease.

6/7/17
DIALOG(R)File 155:MEDLINE(R)

06213476 90002892
Immunotoxins containing glucose oxidase and lactoperoxidase with **tumoricidal** properties: in vitro killing effectiveness in a mouse plasmacytoma cell model.
Stanislawski M; Rousseau V; Goavec M; Ito H
Laboratoire d'Immunologie, Centre National de la Recherche Scientifique, Villejuif, France.
Cancer Res (UNITED STATES) Oct 15 1989, 49 (20) p5497-504, ISSN 0008-5472 Journal Code: CNF

Contract/Grant No.: CA-34183, CA, NCI; CA-40216, CA, NCI; TWO4496
Comment in N Engl J Med 1992 Apr 23;326(17):1163-4
Languages: ENGLISH
Document type: JOURNAL ARTICLE

BACKGROUND. The use of autologous bone marrow transplantation is increasing in the management of advanced cancers. Many investigators have attempted to "purge" autologous marrow of residual **tumor** cells because of concern that reinfused **tumor** cells might contribute to relapse. The efficacy of purging remains unproved. METHODS. We performed clonogenic assays in a **tumor cell** line in culture to determine the efficiency of immunologic purging. Amplification by the polymerase chain reaction (PCR) was used to detect residual lymphoma cells before and after purging of bone marrow from 114 patients with B-cell non-Hodgkin's lymphoma in whom a translocation (t(14;18] that could be amplified by PCR was detected at the time of their initial evaluation. RESULTS. Immunologic purging in vitro resulted in a 3-to-6-log destruction of cells in the **tumor cell** line. Residual lymphoma cells were detected by PCR in the bone marrow of all patients before purging. No lymphoma cells could be detected in the marrow of 57 patients after purging. Disease-free survival was increased in these 57 patients as compared with those whose marrow contained detectable residual lymphoma (P less than 0.00001). The ability to purge residual lymphoma cells was not associated with the degree of bone marrow involvement (P = 0.4494) or the previous response to therapy (P = 0.1298). CONCLUSIONS. The inability to purge residual lymphoma cells was the most important prognostic indicator in predicting relapse. These results provide evidence of the clinical usefulness of **ex vivo** purging of autologous bone marrow in the treatment of patients with lymphoma and suggest that the reinfusion of malignant cells in autologous marrow contributes to relapse

6/7/15
DIALOG(R)File 155:MEDLINE(R)

06687510 91172571
Treatment of high-risk solid **tumors** of childhood with intensive therapy and autologous bone marrow transplantation.
Seeger RC; Reynolds CP
Department of Pediatrics, Children's Hospital of Los Angeles, University of Southern California School of Medicine.
Pediatr Clin North Am (UNITED STATES) Apr 1991, 38 (2) p393-424, ISSN 0031-3955 Journal Code: OUM
Contract/Grant No.: CA22794, CA, NCI; CA44904, CA, NCI; CA02649, CA, NCI; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

Autologous bone marrow transplantation (ABMT) allows delivery of intensive, marrow-ablative chemotherapy or chemoradiotherapy to children with high-risk solid **tumors** . Results from several studies of neuroblastoma suggest that outcome is improved by ABMT; however, relapses can occur months to years after complete clinical remission. Other high-risk **tumors** including peripheral neuroepithelioma, Ewing's sarcoma, rhabdomyosarcoma, Wilms' **tumor**, and brain **tumors** also appear to be responsive to intensive marrow-ablative therapy, although few studies have been reported. For **tumors** that can metastasize to marrow, a sensitive method is necessary for detecting **tumor cell** contamination. Immunocytologic analysis with monoclonal **antibodies** can identify one neuroblastoma cell per 10(5) normal marrow cells; this method also is applicable to other **tumors** with appropriate **antibodies**. **Ex vivo** removal (purging) of

Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have tested the **tumoricidal** potency of enzyme immunotoxins constructed of **antibodies** conjugated to glucose oxidase and to lactoperoxidase. Murine plasmacytoma cells were targeted in vitro with the use of affinity-purified rabbit anti-plasmacytoma membrane **antibodies** (conjugated to glucose oxidase or lactoperoxidase) or rabbit serum raised against plasmacytoma microsome membranes followed by goat anti-rabbit immunoglobulin conjugates (to glucose oxidase or lactoperoxidase). Cytotoxicity was generated subsequently by incubation of the washed cells in a medium supplemented with glucose and sodium iodide, which were the substrates of these enzymes. This resulted in the presumed metabolic release of highly toxic reduced oxygen species and iodinated derivatives. Targeting of **tumor** cells with both conjugates, as opposed to one of them alone, produced a synergistic killing effect. The gain of specific versus unspecific cytotoxicity was upwards of 10,000-fold. The killing rates were elevated (t10 values less than 30 min) and linear over time. The resultant reduction in **tumor cell** viability was in the order of 5 to 6 logs after only 20 to 90 min of incubation in the glucose/NaI medium. Cytotoxicity was enhanced by the gamma-glutamyl cysteine synthetase inhibitor buthionine-S,R-sulfoximine and by the glutathione reductase inhibitor 1,3-bis(2-chloroethyl)-1-nitrosourea, while catalase was inhibitory. The results suggest that these enzyme immunotoxins may be suitable for the **ex vivo** purging of autologous bone marrow grafts.

6/7/18
DIALOG(R)File 155:MEDLINE(R)

05830115 90028759
Elimination of drug-resistant myeloma **tumor cell** lines by monoclonal anti-P-glycoprotein **antibody** and rabbit complement.
Kulkarni SS; Wang ZM; Spitzer G; Taha M; Hamada H; Tsuruo T; Dicke KA
Department of Hematology, University of Texas M.D. Anderson Cancer Center, Houston 77030.
Blood (UNITED STATES) Nov 1 1989, 74 (6) p2244-51, ISSN 0006-4971 Journal Code: A8G
Contract/Grant No.: CA 23077, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The effectiveness of **ex vivo** chemotherapy with drugs, such as vincristine, etoposide, and Adriamycin (doxorubicin, Adria Labs, Columbus, OH) for elimination of residual **tumor** cells from human bone marrow grafts could be undermined by the presence of multidrug-resistant **tumor** cells in the bone marrow. Therefore, to supplement chemoseparation, we investigated whether MRK-16, a monoclonal **antibody** (MoAb) to the surface moiety of multidrug resistance-associated P-glycoprotein antigen, can eliminate drug-resistant **tumor** cells in the presence of rabbit complement (RC). Two doxorubicin (DOX)-resistant human myeloma **tumor cell** line, 8226/DOX40 (resistant to 4 x 10(-7) mol/L DOX) and 8226/DOX6 (6 x 10(-8) mol/L DOX) with high and low amounts of cell surface P-glycoprotein, respectively, and the drug-sensitive parent cell line 8226/S were used as **tumor** models in this study. Using the limiting dilution assay, we have shown that three cycles of treatment with 25 micrograms/mL of MRK-16 MoAb and a 1:4 final dilution of RC eliminated 2.90 +/- 0.10 logs of 8226/DOX40 cells and 1.94 +/- 0.18 logs of 8226/DOX6 cells. One and two cycles of treatment were less effective, eliminating 0.47 +/- 0.40 and 1.94 +/- 0.36 logs of 8226/DOX40 and 0.12 +/- 0.20 and 1.63 +/- 0.58 logs of

8226/DOX6 cells, respectively. The 8226/S cell growth was unaffected by one to three cycles of treatment. The cell kill was not impaired when the **antibody** plus complement treatment was carried out on a mixture of 8226/DOX40 or 8226/DOX6 cells with a ninefold excess of irradiated bone marrow mononuclear cells (MNCs). The three cycles of treatment with **antibody** plus complement did not adversely affect granulocyte-macrophage colony-forming unit (GM-CFU) survival in hematologically normal marrows (92.5% to 104% survival) or in myeloma patient marrows (85% to 100%). These results show that it is possible to eliminate drug-resistant myeloma **tumor cell** lines from the admixed human bone marrow by treatment with MRK-16 MoAb plus RC. This method could prove to be effective for elimination of other drug-resistant **tumor cell** lines including those of leukemia and solid **tumors** , and will be further useful for supplementing chemopurging, and immunopurging of bone marrow with other antitumor cell **antibodies** .

6/7/19
DIALOG(R)File 155:MEDLINE(R)

05795962 90090469
Effect of interleukin-2 on the **ex vivo** growth of human myeloma cells.
Peest D; de Vries I; Holscher R; Leo R; Deicher H
Abteilung Immunologie und Transfusionsmedizin, Medizinische Hochschule Hannover, Federal Republic of Germany.
Cancer Immunol Immunother (GERMANY, WEST) 1989, 30 (4) p227-32, ISSN 0340-7004 Journal Code: CN3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Short-term cultures containing bone marrow mononuclear cells from multiple myeloma patients secrete monoclonal immunoglobulin- and beta 2-microglobulin into the supernatant, which can be measured quantitatively in an enzyme-linked immunosorbant assay. In this system, the addition of interleukin-2 was shown to induce **tumor cell** regression in the cultures from 10 out of 14 multiple myeloma patients in a dose-dependent manner. Marker analyses of culture cell populations indicate that OKT3 **antibody** or interleukin-2 did not directly act on the malignant clone but augmented autologous T lymphocytes, which were responsible for the regression of **tumor** cells in the cultures.

6/7/20
DIALOG(R)File 155:MEDLINE(R)

05394903 89001183
Elimination of myeloma cells from bone marrow by using monoclonal **antibodies** and magnetic immunobeads.
Shimazaki C; Wisniewski D; Scheinberg DA; Atzpodien J; Strife A; Gulati S ; Fried J; Wisniewolski R; Wang CY; Clarkson BD
Laboratory of Hematopoietic Cell Kinetics, Memorial Sloan-Kettering Cancer Center, New York 10021.
Blood (UNITED STATES) Oct 1988, 72 (4) p1248-54, ISSN 0006-4971 Journal Code: A8G
Contract/Grant No.: CA-20194, CA, NCI; CA-08478, CA, NCI; CA-19117, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The efficacy of immunomagnetic beads to purge human myeloma cells from bone marrow **ex vivo** was evaluated. The optimal conditions for purging were studied first by using three myeloma cell lines: RPMI-8226, SKO-007, and SKMM-2. Myeloma cells labeled with the vital fluorescent dye Hoechst 33342 were admixed with normal bone marrow cells, and two monoclonal **antibodies** reactive with the myeloma cells (PCA-1 and BL-3) were added alone or in combination with the cells. Magnetic beads coated with goat antimouse immunoglobulin G were then added, and the **tumor** cells to which beads were attached were separated from the mixture with a magnet. The efficacy of **tumor cell** removal was dependent on the bead-to-**tumor** ratio; a ratio of more than 500 was optimal in the presence of excess normal marrow cells. The combination of monoclonal **antibodies** PCA-1 and BL-3 increased the **tumor cell** removal as compared with either **antibody** alone. Two cycles of treatment were more effective than one cycle was. Under optimal conditions, 2.3 to 4 logs of **tumor** cells could be removed from the mixture containing 10% myeloma cells without a significant loss of normal hematopoietic progenitors as measured by CFU-GM, CFU-GEM, and BFU-E. When the efficacy of this procedure was tested on fresh bone marrow from patients with multiple myeloma (MM) by using the combination of PCA-1, BL-3, and J-5, 1.6 to 2.5 logs of **tumor** cells could be removed by one cycle of treatment, even from marrows containing less than 10% myeloma cells. These observations support the use of monoclonal **antibody** combinations and immunobeads as a reliable and nontoxic method to eliminate contaminating myeloma cells **ex vivo** in preparation for autologous bone marrow transplantation in patients with MM.

6/7/21
DIALOG(R)File 155:MEDLINE(R)

05235186 86105992
Pathogenesis of metastatic disease: implications for current therapy and for the development of new therapeutic strategies.
Poste G
Cancer Treat Rep (UNITED STATES) Jan 1986, 70 (1) p183-99, ISSN 0361-5960 Journal Code: CNM
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW
Different **tumor cell** subpopulations coexisting within the same **tumor** exhibit varied susceptibilities to antineoplastic agents. **Tumor cell** heterogeneity is now recognized as the principal cause of treatment failure in cancer, and is a formidable obstacle to effective therapy and to the development of drug delivery systems for selective targeting of antineoplastic agents to **tumor** cells. Recent insights into the genesis of **tumor cell** heterogeneity during progressive **tumor** growth reveal new complexities that raise challenging questions about the adequacy of certain approaches to the current therapy of metastatic disease and impose challenging criteria for the development of improved therapeutic strategies. Many of the experimental approaches used in the search for new antineoplastic agents and targeted drug delivery systems ignore the pathogenesis of metastasis and the problem of **tumor cell** heterogeneity. The adoption of more relevant assay systems is an urgent priority. These include the greater use of metastatic **tumor** models and the increased use of human **tumor** cells to replace rodent cell systems which have been of limited predictive value in identifying effective anticancer agents. In contrast to current strategies for the development of new antineoplastic drugs which seek to identify agents with activity against a broad range of histologically diverse **tumors** , greater success may be achieved by

seeking agents active only against specific cell lineages. Many established human **tumor cell** lines may not be suitable for this purpose because of extensive phenotypic change produced by prolonged passage **ex vivo**. Development of histiotype-specific human **tumor cell** screens will require an extensive research effort to identify target cells that display demonstrable phenotypic relatedness to **tumor** cells in neoplastic lesions. Major advances in the therapy of metastatic disease are considered unlikely in the next few years, and progress will stem from improved use of existing agents in refined combination therapy protocols in which greater attention is given to the duration, frequency, and sequence of therapy with different agents to limit emergence of **tumor cell** variants resistant to one or more antineoplastic agents. Advances in molecular biology offer exciting prospects for the identification of new therapeutic targets in human **tumor** cells, for the induction of alterations in **tumor** cells that could serve as therapeutic targets, and for the elucidation of the mechanisms responsible for the rapid phenotypic diversification of **tumor** cells.(ABSTRACT TRUNCATED AT 400 WORDS) (64 Refs.)

6/7/22
DIALOG(R)File 155:MEDLINE(R)

04137146 86027609
Delivery of ricin and abrin A-chains to human carcinoma cells in culture following covalent linkage to monoclonal **antibody** LICR-LOND-Fib 75.
Forrester JA; McIntosh DP; Cumber AJ; Parnell GD; Ross WC
Cancer Drug Deliv (UNITED STATES) Fall 1984, 1 (4) p283-92, ISSN 0732-9482 Journal Code: CLT
Languages: ENGLISH
Document type: JOURNAL ARTICLE
With the object of generating specific cytotoxic agents, we have prepared covalent conjugates of the A-chains of ricin and of abrin with monoclonal **antibody** LICR-LOND-Fib 75 and investigated their toxicity toward a human **tumor cell** line in culture. Both conjugates proved to be potent cytotoxins toward cells carrying the appropriate antigen. The agent containing abrin A-chain was toxic at a significantly lower concentration and exerted its maximum effect more rapidly than the one containing ricin A-chain. Inclusion of chloroquine in the incubation medium significantly enhanced the toxic action of both conjugates without loss of immunospecificity. Because of the widespread occurrence on human **tumor cell** lines of the antigen recognized by Fib 75, these conjugates, particularly the one containing abrin A-chain, may find application in freeing human bone marrow **ex vivo** of infiltrated **tumor** cells prior to reinfusion as an autograft.
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       12jul99 08:13:22 User208709 Session D445.3
            $9.61    3.205 DialUnits File155
               $1.00  5 Type(s) in Format  3
               $8.80  44 Type(s) in Format  7
            $9.80  49 Types
    $19.41  Estimated cost File155
            FTSNET   0.116 Hrs.
    $19.41  Estimated cost this search
    $19.68  Estimated total session cost   3.329 DialUnits
Logoff: level 99.05.27 D  08:13:22
```